Pancreatic Ductal Adenocarcinoma and Its Variants

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KEYWORDS

• Pancreatic ductal adenocarcinoma • Pancreatic cancer • PDAC • Ductal • Adenosquamous • Colloid • Osteoclast

Key points

- Pancreatic cancer was the seventh leading cause of cancer death in the world in the past 3 years.
- There are classic morphologic features to be used for the diagnosis of pancreatic ductal adenocarcinoma.
- There is not an unequivocal immunohistochemical panel for the diagnosis of this tumor.
- Chronic/autoimmune pancreatitis is an important differential diagnosis

ABSTRACT

Pancreatic cancer represents the seventh leading cause of cancer death in the world, responsible for more than 300,000 deaths per year. The most common tumor type among pancreatic cancers is pancreatic ductal adenocarcinoma, an infiltrating neoplasm with glandular differentiation that is derived from pancreatic ductal tree. Here we present and discuss the most important macroscopic, microscopic, and immunohistochemical characteristics of this tumor, highlighting its key diagnostic features. Furthermore, we present the classic features of the most common variants of pancreatic ductal adenocarcinoma. Last, we summarize the prognostic landscape of this highly malignant tumor and its variants.

OVERVIEW

Pancreatic cancer is a lethal malignancy; it was the seventh leading cause of cancer death in the world in the past 3 years, responsible for more than 300,000 deaths per year.[1,2] The 5-year survival of pancreatic cancer is approximately 5%, a figure that has remained constant in recent decades. The most common type among malignant tumors is pancreatic ductal adenocarcinoma (PDAC), an infiltrating neoplasm with glandular differentiation, which is derived from the pancreatic ductal tree. The highest incidence of PDAC is recorded among African Americans and indigenous population in Oceania (approximately 1 per 10,000).[3] Moreover, high-resource countries and urban populations have a higher incidence than low-income countries and rural populations.[3] Studies of migrant populations suggest that environmental and dietary factors play an important role in the etiology.[4] PDAC is associated with nutritional and dietary factors like high intake of fats and obesity, low physical activity, and heavy alcohol drinking.[3,5] However, the best-known risk factor for PDAC is tobacco smoking, which is associated with a 2 to 3 times greater risk than

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in nonsmokers.[6] Other significant conditions associated with a higher risk of PDAC are diabetes mellitus, with a risk of approximately twofold, and a history of chronic pancreatitis, above all if this condition is hereditary, as it is associated with an increased risk of PDAC of more than 10-fold.[7] Clinical features include back pain, jaundice for pancreatic head tumor, unexplained weight loss, pruritus, diabetes mellitus, and occasionally migratory thrombophlebitis, acute pancreatitis, hypoglycemia, and hypercalcemia.[3,8–10] For the radiological study of pancreas, one of the best imaging modalities is represented by computed tomography (CT), in which PDAC appears as a hypodense mass in up to 92% of cases; on endoscopic ultrasonography (EUS), most PDACs are echo-poor and nonhomogeneous.[3,11,12] Variants of conventional PDAC are the following: (1) adenosquamous carcinoma, (2) colloid carcinoma, (3) undifferentiated or anaplastic carcinoma, (4) undifferentiated carcinoma with osteoclastlike giant cells (UCOCGC), (5) signet-ring carcinoma, (6) medullary carcinoma and (7) hepatoid carcinoma.[3,13] Another important entity is represented by carcinomas with mixed differentiation. This heterogeneous group is composed of mixed acinar-ductal carcinoma, mixed acinar-neuroendocrine carcinoma, mixed acinar-neuroendocrine-ductal carcinoma and mixed adeno-neuroendocrine carcinoma (MANEC).[3]

GROSS FEATURES

CONVENTIONAL PANCREATIC DUCTAL ADENOCARCINOMA

Most (60%–70%) PDACs are located in the head of the gland, and the remainder, with a similar rate (approximately 15% each), in the body and/or tail.[11] Generally, PDAC is a solitary lesion, but it may also occasionally present as a multifocal disease.[3,13] PDACs are firm, hard, sclerotic and poorly defined masses, which replace the normal lobular architecture of the gland. The cut surface is usually whitish (**Fig. 1**). Sometimes, a microcystic area can be present, particularly in large tumors; hemorrhage and necrosis are very rare. Most PDACs of the head range from 1.5 to 5.0 cm, whereas PDACs of body/tail are usually larger. PDACs of the head usually invade the common bile duct and/or the Wirsung duct, producing stenosis that results in proximal dilatation of both duct systems. More advanced PDACs in the head can involve the papilla of Vater and the duodenal wall. In the body/tail, PDAC usually causes obstruction of the Wirsung duct, with secondary changes in the upstream pancreatic parenchyma, including retention-cyst formation, duct dilatation, and fibrous atrophy of the parenchyma. At the time of the diagnosis, most PDACs have already spread beyond the pancreatic parenchyma, and are not operable; conversely, the typical TNM status at diagnosis of the operable PDACs is T3N1 (T3 indicates that the tumor has grown outside the pancreas into nearby surrounding tissues, but not yet into major blood vessels or nerves, and N1 indicates the presence of metastasis in regional lymph nodes) highlighting also the rapidity of tumor growth and of metastasis. Common extensions of PDAC of the head are the following: intrapancreatic portion of the common bile duct, peripancreatic or retroperitoneal (posterior lamina) adipose tissue, papilla of Vater, and duodenum. Perineural invasion is a very common mechanism by which PDAC reaches these structures. PDACs of body and tail can first invade spleen, stomach, left adrenal gland, peritoneum, and colon. The lymph nodes most commonly involved by PDAC are the peripancreatic lymph nodes. Furthermore, for PDACs of the head, an important site of metastasis is represented by the chains of lymph nodes along the superior mesenteric and common hepatic arteries, and the hepatoduodenal ligament. For PDACs of body and tail, frequent sites of involvement are the superior and inferior body and tail lymph node groups, and the lymph nodes of the splenic hilus.[3] Metastasis of the para-aortic area is associated with a worse prognosis.[14]

PANCREATIC DUCTAL ADENOCARCINOMA VARIANTS

The variants of conventional PDAC have some peculiar macroscopic aspects, but there are no definitive criteria to distinguish such variants grossly. *Adenosquamous carcinoma* is usually represented by a white-gray firm and multinodular mass (see **Fig. 1**). *Colloid carcinoma* is characterized by large pools of mucin, usually arising in association with an intraductal mucinous papillary neoplasm (IMPN) of intestinal-type (see **Fig. 1**). *Undifferentiated or anaplastic carcinoma* is larger than conventional PDAC but has very similar macroscopic features; *the variant with osteoclastlike giant cells* has very often several foci of hemorrhage and necrosis (see **Fig. 1**). *Signet-ring* and *medullary carcinoma* are grossly very similar to conventional PDAC and *hepatoid carcinoma* is characterized by white-yellowish, multi-lobed masses. Last, mixed carcinomas usually consist in large masses with necrotic foci.